Cogan's syndrome in patients with inflammatory bowel disease–a case series

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Abstract: BACKGROUND: Cogan's syndrome (CSy) is a very rare autoimmune disorder, mainly affecting the inner ear and the eye, and is associated with inflammatory bowel disease (IBD). METHODS: This was a European Crohn's and Colitis Organisation (ECCO) retrospective observational study, performed as part of the CONFER project. A call to all ECCO members was made to report concomitant CSy and inflammatory bowel disease (IBD) cases. Clinical data were recorded in a standardized questionnaire. RESULTS: This international case series reports on 22 concomitant CSy-IBD cases from 14 large medical centres. Mean duration of IBD until diagnosis of CSy was 8.7 years (range 0.0-38.0) and mean age at CSy diagnosis was 44.6 years (range 9.0-67.0). Six patients had underlying ulcerative colitis (UC) and 16 had Crohn's disease. Eleven patients (50%) had active disease at CSy diagnosis. Sixteen patients were under IBD treatment at the time of CSy diagnosis, of whom 6 (37.5%) were on anti-tumour necrosis factor (TNF). Seven out of 10 patients, who were treated for CSy with immunomodulators (mostly with corticosteroids), demonstrated at least partial response. CONCLUSION: This is the largest CSy-IBD case series so far. Although CSy is considered to be an autoimmune disease and is associated with IBD, immunomodulatory IBD maintenance treatment and even anti-TNF therapy do not seem to prevent disease onset. Moreover, IBD disease activity does not seem to trigger CSy. However, vigilance may prompt early diagnosis and directed intervention with corticosteroids at inception may potentially hinder audiovestibular deterioration. Finally, vigilance and awareness may also offer a better setting to study the pathophysiological mechanisms of this rare but debilitating phenomenon.

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Cogan`s Syndrome in Patients With Inflammatory Bowel Disease – a Case Series

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Short title: Cogan`s Syndrome and IBD

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Authorship statement

SRV and JFR conceived the study; SRV, JFR and TG were responsible for analysis and interpretation of data, and drafting of manuscript; MS, KK, CKT, HB, RF, GM, AVW, ABS, HY, CF, CS, RK, GR contributed the cases and were responsible for revision of manuscript as well as for the treatment of the respective patients

Conflict of interest

None declared

Abstract

Background: Cogan`s syndrome (CSy) is a very rare autoimmune disorder, mainly affecting the inner ear and the eye, and is associated with inflammatory bowel disease (IBD). Materials and methods: This was a European Crohn's and Colitis Organization (ECCO) retrospective observational study, performed as part of the CONFER project. A call to all ECCO members was made to report concomitant CSy and IBD cases. Clinical data were recorded in a standardized questionnaire. Results: This international case series reports on 22 concomitant CSy-IBD cases from 14 large medical centers. Mean duration of IBD until diagnosis of CSy was 8.7 years (range 0.0-38.0), and mean age at CSy diagnosis was 44.6 years (range 9.0-67.0). 6 patients had an underlying ulcerative colitis (UC), 16 Crohn`s disease (CD). 11 patients (50%) had active disease at CSy diagnosis. 16 patients were under IBD treatments at the time of CSy diagnosis, of whom 6 (27.3%) were on anti-TNF. 7 out of 10 patients, who were treated for CSy with immunomodulators (mostly with corticosteroids), demonstrated at least partial response. Conclusion: This is the largest CSy-IBD case series so far. Although CSy is considered to be an autoimmune disease and is associated with IBD, immunomodulatory IBD maintenance treatment and even anti-TNF therapy do not seem to prevent disease onset. Moreover, IBD disease activity does not seem to trigger CSy. However, vigilance may prompt early diagnosis and directed intervention with corticosteriods at inception may potentially hinder audiovestibular deterioration. Finally, vigilance and awareness may also offer a better setting to study the pathophysiological mechanisms of this rare, but debilitating phenomena.

Keywords: Cogan`s syndrome, inflammatory bowel disease, Crohn`s disease, ulcerative colitis

Introduction

Cogan`s syndrome (CSy) is a very rare autoimmune disorder, [1] which affects the inner ear and the eyes. [2] Its typical manifestation has been first described in the 1940s. [3] The mainstay of its clinical diagnosis are audiovestibular symptoms resembling Meniere`s disease and ocular inflammation such as interstitial keratitis. [4] In up to 70% of patients, other systemic manifestations such as arthralgia, fever or myalgias are observed with aortitis as the most complicating form. [5] Given the variable onset of symptoms, the possibility of atypical subtypes and the lack of specific laboratory tests, the diagnosis is often challenging, although cases with calcification and narrowing of the vestibular labyrinth and the cochlea on MRI have been recently described. [6,7] Despite its very rare incidence, more than 100 cases have been published in the literature giving increasing insights into different clinical manifestations and disease pathophysiology. [8]

As it is known from several autoimmune disorders, CSy shows an association with inflammatory diseases. Interestingly an assocation between CSy and inflammatory bowel diseases (IBD) such as Crohn`s disease (CD) and ulcerative colitis (UC) has been described in few patients. [7,9-16] Due to systemic manifestations in both CSy and IBD and the challenging diagnosis of CSy, diagnosing CSy in IBD patients seems to be difficult, in particular. Hitherto, a total of 13 patients with both CSy and IBD have been reported. [7,9-16] Moreover, very little is known about the underlying pathophysiological mechanism. Herein, we report a case series of 22 patients suffering from both IBD and CSy. Given the large study population and the inclusion of patients from a total of 14 international large IBD centers, this systematic case series represents a significant contribution to the knowledge about this disease and may reveal a possible pathophysiological association between the two autoimmune-mediated diseases CSy and IBD.

MATERIALS & METHODS

Study design

This European Crohn's and Colitis Organization (ECCO) observational multicenter study retrospectively collected cases across the world through the CONFER (COllaborative Network For Exceptionally Rare case reports) project. The CONFER project was initiated by ECCO in order to specifically identify and report together rare IBD disease associations, which otherwise get seldom reported due to their exceptional rarity. Briefly, the CONFER methodology comprised of selecting a topic worthy of investigation out of case proposals submitted by ECCO members. Once a specific IBD disease association was selected by a steering committee as CONFER project (Cogan`s syndrome and IBD association in the case of the present study), ECCO launched a call to identify similar cases encountered by IBD physicians worldwide.

The call to physicians was made through announcements in the ECCO annual congress and in National IBD meetings across Europe and during several International IBD meetings. In addition, the call for similar cases was disseminated by direct emails to all ECCO members and affiliated physicians and on the ECCO website and in the ECCO eNews. Physicians were then prompted to report their case to the CONFER database using a pre-determined standardized Case Report Form (CRF). The call for the present case-series was entitled "Cogan`s syndrome in patients with IBD".

Patients and procedures

All adult IBD patients (age > 16 years) with CSy diagnosis throughout the course of IBD or prior to its diagnosis were eligible for inclusion in this study. CSy diagnosis was made based on clinical presentation according to prior case reports and reviews. [1,17] Data were

collected by a CRF, which was divided into two main sections. Section 1 included patient (epidemiological data, past medical history, alcohol consumption/smoking, family history) and disease (IBD subtype, date of diagnosis, Montreal classification, extraintestinal manifestations and IBD treatment) characteristics. Section 2 included a description of CSy with regards to diagnosis: IBD treatment at CSy diagnosis, CSy related symptoms and treatments (including cochlea implantation and treatment outcome). Relevant laboratory tests were also recorded.

Statistics

For the statistical analysis, the IBM Software SPSS Statistics Version 22.0.0 (2013 SPSS Science, Inc., Chicago, IL) was used.

RESULTS

Patients` background information

We identified a total of 22 patients from 14 medical centers across the world. 16 patients had CD and 6 patients UC. 4 of the 6 UC patients had a pancolitis (Montreal classification E3, 66.7%), while most of the CD patients showed either ileal (7 patients, 43.8%) or ileocolonic (6 patients, 37.5%) disease localisation. Mean age at enrolment was 46.6 years (range 19.0-74.0) with a mean age at IBD diagnosis of 34.7 years (range 1.0-59.0). 13 were female (59.1%), 18 patients were Caucasians (85.7%) and 2 patients (9.1%) had a positive family history for IBD with 1 patient reporting a mother with UC and two siblings with CD and another patient reporting a sister with CD. Only 3 patients (13.6%) were current smokers, while 4 reported to have smoked in the past with a mean cessation time of 15.8 years (3.0-29.0) at study inclusion. Prior reported IBD treatments mainly consisted of 5-aminosalicylic acid (5-ASA) (17 patients, 77.3%), systemic steroids (13 patients, 59.1%) and azathioprine/6-MP (AZA/MP) (12 patients, 54.4%). A total of 9 patients (40.9%) received at least one dose of anti-TNF therapy. 8 patients (36.4%) underwent prior surgery (proctocolectomy in UC, partial ileal or jejunal resection and rectal abscess drainage). Patients` characteristics are shown in table 1. 4 of the patients had been reported previously in a case series investigating the association between CSy and IBD. [9] CSy disease characteristics are summarized in table 2.

Cogan`s syndrome and IBD

All diagnoses of CSy (n=22) were made after IBD was diagnosed. Mean duration of IBD until diagnosis of CSy was 8.7 years (0.0-38.0) with a mean age at diagnosis of 44.6 (range 9.0-67.0). Mean time from first hearing impairment until CSy diagnosis was 1 year (range 0-15),

indicating a significant duration of uncertainty before CSy diagnosis. Indeed, in only 8 patients (36.4%) diagnosis could be definitely made, while in thirteen patients diagnosis was probable and in 1 patient remained uncertain. 11 patients (50%) had active disease at CSy diagnosis and a total of 16 patients (72.7%) were currently under IBD treatment (table 2). The most frequently reported therapies were: 5-ASA (8 patients, 36.4%), AZA/MP (3 patients, 13.6%) and systemic steroids (2 patients, 9.1%). A total of 6 patients (27.3%) were on anti-TNF treatment with median time interval between first anti-TNF administration and first audiovestibular or ocular symptoms of 19.5 months (range 4.7-46.0). Median time interval to CSy diagnosis was 24.2 months (23.0-47.0). Diagnosis of CSy was made based on ORL evaluation, audiometry, ophthalmology evaluation and cranial imaging. 9 patients (40.9%) reported audiovestibular symptoms first, while in 6 patients (27.3%) ocular involvement occured first. 2 patients (9.1%) reported prodrome symptoms of viral infection preceding onset of CSy. Among the most frequently reported CSy symptoms were those related to the audiovestibular system with tinnitus, impaired hearing or hearing loss even to the point of bilateral deafness, and vertigo. Ocular symptoms were reported in 9 patients with most of them suffering from interstital keratitis. Other systemic symptoms such as headache, arthralgias, dizziness or fatigue were also frequently reported, while neurologic deficits were very rare with hemiparesis and nystagmus in only 1 patient. In addition, only 1 patient reported vascular complications (such as aortitis). None of the ongoing audiovestibular or neurologic symptoms were attributed to prior or concomitant anti-TNF treatment. Reported CSy symptoms are summarized in table 3.

Treatment for CSy was initiated in 10 patients (45.5%) with allmost all of them treated with systemic corticosteroids. 1 patient was treated with methotrexate alone, while 2 of the

other 9 patients were treated with cyclophosphamide and AZA, respectively, in addition to oral corticosteroids. Of those treated, 7 patients (70%) showed at least a partial response or stabilization of the disease with 1 additional patient still under therapy with response awaiting. Cochlea implantation was performed in a total of 4 patients. Laboratory testing was normal in most of the patients with abnormal, but only slightly elevated CRP in 7 patients (mean 8.2 g/dl, range 1.4-18.0) and elevated blood sedimentation reaction in only 5 patients (mean 56 mm/h, range 45-70).

Discussion

CSy is a very rare autoimmune disease affecting the inner ear, which may ultimately result in complete (bilateral) deafness. [18] CSy typically affects young Caucasian adults [8] with a median age of 25 years at disease onset and without gender specific predilection, [19] which is in impressive contrast to the relatively older age (median age at CSy onset of 44.6 years) and female preponderance in this case series – even if the diagnostic delay of 1 year (with a maximum of 15 years) is taken into consideration. Other autoimmune disorders occur in 15-30% of CSy patients. [2] Up to date, only 13 patients have been reported with the concomitant diagnosis of IBD and CSy. In the vast majority the onset of CSy precedes IBD manifestation. [7,12] Herein, we report on 22 IBD patients, who were all diagnosed with CSy after IBD manifestation with a median time from IBD to CSy diagnosis of 8.7 years and a broad range of 0.0 years up to 38.0 years. Little is known about this assocation between CSy and IBD and even less is known about its pathogenetic mechanisms. Given the extremely rare incidence of CSy with not exceeding 250 cases reported in the medical literature, [18] the identification of 22 IBD patients with concomitant CSy herein may suggest a stronger association between these two entities of dysregulated immunity than previously thought. However, as it is has been shown in several cases treated with anti-TNF for inflammatory diseases such as IBD or rheumatoid arthritis, [20-22] TNF antibodies themself may trigger neurologic symptoms, which may include CSy-like symptoms, via a demyelinating process comparable to multiple sclerosis. Nevertheless, none of the ongoing audiovestibular or other neurologic manifestations were attributed to anti-TNF in the 9 patients with prior or concomitant anti-TNF therapy.

CSy is thought to be an autoimmune disease that is mediated by a hypersensitivity response to infectious agents associated with vasculitis. [1,23,24] An immediate preceding upper respiratory tract infection may lead to cross-reactive auto-antibodies, in particular. Interestingly, some case reports could show elevated titres against C. trachomatis and C. pneumoniae. [10,25] However, in this case series only 2 patients reported prodrome symptoms of viral infection preceding CSy diagnosis. Several antibodies directed against corneal antigens and antigens on endothelial cells and in the inner ear have been identified. [1,16,26,27] One of them with reactivity against the Cogan-peptide, which shares sequence homology with CD148 and connexin 26 (expressed on endothelial cells and in the inner ear), is able to transfer the disease in animal models. [28] Moreover, histopathological examinations revealed a lymphocytic and plasma cell infiltration to the corneal and cochleal tissue suggesting a cell-mediated autoimmune reactivity. [29] This is further supported by the fact that CSy patients` lymphocytes are activated when exposed to corneal and inner ear antigens. [14,23,30] In contrast, IBD – with the two main subtypes CD and UC – is not regarded as a classical autoimmune disorder and its etiopathogenesis is yet incompletely understood. Nevertheless, it is considered to be a multifactorial disease, which arises from a complex interplay between genetic, environmental and immunological factors with an abnormal host immune response to environmental stimuli. [31] So far, no common pathogenetic mechanisms between CSy and IBD have been identified. To the best of our knowledge, there are no shared susceptibility genes, auto-antibodies or environmental factors. Interestingly, IBD disease activity does not seem to trigger CSy given the finding, that 50% had quiescent CD or UC at CSy diagnosis in this case series. One may assume that the association between these entities is no more than a cluster of two disorders with a dys-regulated immune system rather than one common underlying autoimmune process.

Success of CSy treatment depends on its early diagnosis and early initiation of systemic corticosteroids, which are considered first line treatment in the presence of inner ear pathology, severe inflammation of the eye and/or systemic vasculitis. [17] If treatment is started within the very first two weeks after hearing loss, more than 50% of the patients show some improvement, while only 8% will improve if treatment is started later. [10,19,32] Combination with other immunosuppressants such as cyclosporine or methotrexate may even improve disease course. [9,33,34] Recently, anti-TNF treatment (with infliximab in particular) has been reported to be of some effect. [35-38] However, this efficacy seems to be limited, which is consistent with our finding that 6 patients developed CSy during treatment with an anti-TNF antibody. Limited response rates of immunomodulatory treatment is also reflected in the fact that 16 patients were diagnosed with CSy despite IBD maintenance treatment. Given a relatively restrictive therapeutic approach in our 22 patients with only 10 treated with immunomodulators, treatment success rate (70% partial response) was higher than in the literature. No anti-TNF treatment was performed. Remarkably, disease progression was observed in all other patients ultimately leading to uni- or even bilateral deafness in 13 of them with 4 patients requiring a cochlea implantation as ultima ratio.

However, as suggested by Scharl et al, [9] association between CSy and IBD may be even stronger than previously thought. Given the rapid progression of CSy ultimately leading to (bilateral) deafness, one should consider this very rare diagnosis in IBD patients complaining of unspecific audiovestibular symptoms such as dizziness and hearing loss and/or ocular inflammation. Although CSy is considered to be an autoimmune disease,

immunomodulatory IBD maintenance treatment and even anti-TNF antibodies do not seem to prevent disease onset. Moreover, IBD disease activity does not seem to trigger CSy. However, early diagnosis is key and early initiation of systemic corticosteroids in selected patients may lead at least to a partial response and audiovestibular improvement. Otherwise, disease progresses rapidly ultimately leading to uni- or even bilateral deafness. In conclusion, vigilance may prompt early diagnosis and directed intervention with corticosteroids at inception may potentially hinder audiovestibular deterioration. Finally, vigilance and awareness may also offer a better setting to study the pathophysiological mechanisms of this rare, but debilitating phenomena.

	Mean (range), n=22
Age (in years)	46.6 (19.0-74.0)
Sex	
- female	13 (59.1%)
- male	9 (40.9%)
IBD (UC/CD)	6 (27.3%) / 16 (72.7%)
Age at diagnosis (in years)	34.7 (1.0-59.0)
Race	
- Caucasian	18 (81.8%)
- Asian	1 (4.5%)
- Black	1 (4.5%)
- Ashkenazi Jew	1 4.5%)
Geographic spread	
- Israel	6 (27.3%)
- Germany	5 (22.7%)
- Greece	5 (22.7%)
- Poland	3 (13.6%)
- Brasil	1 (4.5%)
- Denmark	1 (4.5)
- Switzerland	1 (4.5%)
Positive family history for IBD	2 (9.1%)
Smoking: current/past/never	3 (13.6%) / 4 (18.2%) / 15 (68.2%)
Prior surgery	8 (36.4%)
Prior anti-TNF treatment	9 (40.9%)

Table 1: Patient demographics and IBD characteristics

	Mean (range), n=22
Mean age at diagnosis (in years)	44.6 (9.0-67.0)
Time from first hearing impairment to CSy diagnosis (in years)	1 (0-15)
Time from IBD to CSy diagnosis	8.7 (0.0-38.0)
Patients under IBD treatment at diagnosis	16 (72.7%)
Patients under anti-TNF treatment at diagnosis	6 (27.3%)
Patients with active IBD at diagnosis	11 (50%)
Treatment for CSy	10 (45.5%)

Table 2: IBD and CSy characteristics

Symptoms	Number of patients (n=22)
Impaired hearing	18 (81.8%)
Tinnitus	17 (77.3%)
Hearing loss	16 (72.7%)
Fatigue	16 (72.7%)
Headache	15 (68.2%)
Vertigo	13 (59.1%)
Dizziness	13 (59.1%)
Sensation of fullness of ear, ear pain	10 (45.5%)
Arthralgia	10 (45.5%)
Deafness (bilateral)	9 (40.9%)
Interstitial keratitis	6 (31.8%)
Meniére-like attacks	5 (22.7%)
Myalgia	4 (18.2%)
Conjunctivitis	3 (13.6%)
Fever	3 (13.6%)
Arthritis	3 (13.6%)

Table 3: Frequency of CSy symptoms

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Patient	Sex	Age	IBD	IBD (type)	Disease extent	IBD therapy before CS	CS	IBD to CS (in years)	Audiologic symptoms	Vestibular symptoms	Ocular symptoms	Under IBD treatment	Active IBD at CS diagnosis
1	m	56	56	CD	A3, L1, B2	ASA, AZA			Bilateral deafness	Menière	Conjunctivitis	none	
2	m	52	37	UC	E2	ASA, Steroids	43	5	Bilateral deafness	Tinnitus, vertigo		ASA	Active
3	f	35	18	UC	E1	ASA	34	1.25	Sudden hearing loss	none		ASA, steroids	Active
4	f	64	59	CD	A3, L3, B1	ASA, MTX, TNF	64	5.5	Bilateral deafness	Menière, tinnitus		TNF	Quiescent
5	f	40	25	CD	A2, L1, B1	ASA, Steroids	40	16	Bilateral hearing loss	Meniére, tinnitus, vertigo		none	Quiescent
6	f	24	13	CD	A1, L2, B3	ASA, Steroids, AZA, TNF (2)	24	12	Deafness	none		none	Quiescent
7	f	26	1	CD	A1, L3, B2	ASA, Steroids, AZA, MTX, TNF		5	None	Menière		none	Quiescent
8	m	59	57	CD	A3, L1, B1	AZA	58	0.5	Bilateral deafness	Menière, tinnitus, vertigo	IK	AZA	Active
9	f	64	46	CD	A3, L1, B2	ASA, AZA	63	1.33	Sudden bilateral hearing loss	Menière, tinnitus, vertigo		ASA	Quiescent
10	m	54	13	CD	A1, L1, B3	ASA, Steroids, MTX, TNF (2)	52	38	Bilateral deafness	Menière, tinnitus, vertigo		TNF	Active
11	f	19	7	CD	A1, L4, B2	ASA	9	3	Bilateral deafness	unkown		ASA	Active
12	m	61	44	CD	A3, L3, B3	ASA, Steroids, TNF	61	16	Sudden hearing impairment	vertigo	IK, conjunctivitis	TNF	Active
13	m	39	39	CD	A2, L1, B1	none	38	0	Deafness	Menière		none	Active
14	f	45	49	CD	A2, L3, B2	ASA, AZA, TNF	44	4	Deafness	Menière, vertigo	IK, conjunctivitis	ASA	Quiescent
15	f	56	50	CD	A3, L2, B1	ASA, Steroids	54	4	Deafness	none	IK	ASA	Quiescent
16	m	74	55	UC	E3	ASA, Steroids, AZA	67	21	Hearing loss	Menière	IK	ASA, steroids	Active
17	f	43	39	CD	A2, L3, B2	ASA,	43	5	Bilateral deafness	Menière,		TNF	Quiescent

						Steroids, AZA, MTX, TNF				vertigo			
18	m	40	32	CD	A2, L1, B1	Steroids, AZA, MTX, TNF (2)	40	7	Deafness	Menière		AZA, TNF	Quiescent
19	m	29	26	CD	A2, L3, B3	TNF	27	1	Ear pain	Menière	scleritis	TNF	Active
20	f	46	36	UC	E3	ASA, Steroids, AZA, MTX	40	4	Ear pain	Menière	IK, progressive worsening of visual sense	ASA, Budesonide	Active
21	f	52	44	UC	E3	ASA, Steroids, AZA	51	11	Deafness	Menière		NA	
22	f	48	17	UC	E3	Steroids, AZA	39	22	Ear pain	Menière, vertigo	IK	AZA	Active

Supplementary Table 1: Patient characteristics of the 22 described patients. The columns IBD and CS indicate the year, when the respective diagnosis was established. Abbreviations: m=male; f=female; UC=ulcerative colitis; CD=Crohn`s disease; ASA=5-aminosalicylic acid, AZA=azathioprine; MTX=methotrexate; TNF=anti-TNF therapy